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Letter to the editor

Letter to Editor "Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and MicroRNAs": Important concerns on the validity of this article

We thank the new editor-in-chief of Food and Chemical Toxicology (FCT) journal for giving us the opportunity to present our contradictions to readers and to the scientific community about the review by Seneff et al. titled "*Innate immunosuppression by SARS-CoV-2 mRNA vaccinations: the role of G quadruplexes, exosomes and microRNAs*" (Seneff et al., 2022). The Seneff et al. paper is still available without any note of editorial concern and has been widely read, propagated, and cited despite several gross errors observed. Public health consequences of publishing claims like "*billions of lives are potentially at risk*" with COVID-19 mRNA vaccines in a renowned scientific journal are not anecdotal, especially when the article is widely disseminated among general public. It is indeed the second most shared paper of the journal according to Altmetric data, with an attention score of 18541, 2nd/4980 outputs from the FCT Journal in 2022. With such high metrics, we could expect a paradigm-breaker article. In details, the authors claim that mRNA COVID-19 vaccines are responsible for the "*suppression of type I interferon responses*" resulting "*in impaired innate immunity*" and therefore that they "*potentially cause increased risk to infectious diseases and cancer*". Such strong claims probably explain the public attention raised by this article, but these assertions are not supported by the cited literature, the suggested mechanisms rely on a cascade of improbable and unsupported hypotheses.

In Table 1, we present a non-exhaustive list of major misunderstandings of the literature cited in this Letter. The authors rely on hypothetical physiological disturbances induced by Covid-19 vaccination. For example, they suggest a possible increased risk of occurrence for various cancers which has not been published so far (Corti et al., 2022); in contrast, vaccination is still highly recommended for patients with cancer (Barrière et al., 2022). No causal relationship can be established between the biological mechanisms described by the authors and the alleged effects of mRNA vaccines. Some claims came from the erroneous interpretations of the Vaccine Adverse Events Database (VAERS). The misuse of this database has extensively been described (Calac et al., 2022; Antivaccine activists use a government, 2023). In addition, the analysis proposed by the authors only takes into account the relative values of the occurrences of descriptive adverse events for SARS-COV-2 or non–SARS-COV-2 vaccines without taking into account either the number of injections for each vaccine or the differences in the accuracy of the pharmacovigilance. Thus, no conclusion can be drawn from this analysis. To date, no analysis of the data from the VAERS database supporting the hypothesis of a significant increased mortality secondary to vaccination is available (Singh et al., 2022a). Anti-SARS-CoV-2 vaccination still has a very favorable risk-benefit ratio, saved and will save lives (Arbel et al., 2022; Watson et al., 2022; Haas et al., 2021).

Our collective is not against scientific debate and controversy. Strong claims require strong evidence, especially when published in a journal with such a high impact factor. Fortunately, to our knowledge, no publication has reported an increased risk of cancer after COVID-19 mRNA vaccination. Furthermore, these vaccines are still highly recommended for patients with active cancer undergoing treatment without any particular contraindications.

Seneff et al.'s paper resembles a pre-established hypotheses with cherry-picked cell line dependent mechanisms that do not occur in a real-life setting. It is not supported by actual and strong data. Actually, it lacks the scientific rigor required in such a context and leads to science denial with all the bad consequences associated with vaccine hesitancy. We therefore strongly recommend that the new editor to retract this paper and put an end to the harm caused to public health, getting back to a sane scientific debate where sufficient evidence is required to publish ground-breaking scientific papers.

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Table 1
Summary of some bibliography misunderstandings.

Ref	Quote	Misunderstandings
Liu et al. (2021)	"*Vaccination has also been demonstrated to suppress both IRF7 and STAT2*"	This reference only focuses on one non-mRNA vaccine (inactivated SARS-CoV-2 Vaccine (Vero Cell)) and is thus irrelevant to the authors' focus on mRNA vaccines.
Goldman et al. (2021)	*"The case study described earlier in this paper strongly supports the hypothesis that these injections induce accelerated lymphoma progression in follicular B-cells"*	A causal link cannot be established based on a single case study as referred to in the quoted article (which reports a case of post-vaccine T angio-immunoblastic lymphoma and not B- follicular NHL). No increase of vaccine induced lymphomas have been reported so far. Anti-SARS-CoV-2 vaccines, on the contrary, are known to be weakly immunogenic in patients with lymphoid hemopathy, especially if they are treated with anti-CD20 monoclonal antibodies (Re et al., 2022)
Karikó et al. (2005)	"*Human cells recognize viral RNA as foreign, and this leads to upregulation of type I IFNs*"	Reference is not specific to viral RNA but describes an upregulation that occurs with "a variety of natural RNAs". The paper is dedicated to the hypothesis "*that nucleoside modification suppresses the immune-stimulatory effect of RNA*" thus giving evidence that could reduce the concerns of the authors when designing future mRNA vaccines. Actually, this paper opposes the author's hypothesis since mRNA vaccines have been designed with pseudo-uridines on purpose.
Forni and Mantovani (2021)	As the authors declared: "*Due to the short development time and the novelty of the technologies adopted, these vaccines will be deployed with several unresolved issues that only the passage of time will permit to clarify*"	The reference mainly emphasizes that "*Technical problems connected with the production of billions of doses and ethical ones connected with the availability of these vaccines also in the poorest countries, are imminent challenges facing us. It is our tenet that in the long run more than one vaccine will be needed to ensure equitable global access, protection of diverse subjects and immunity against viral variants*." In this context, the pledges put forward both by pharmaceutical companies and the director of the US Objective Warp Speed (Cohen, 2020) to keep rigorous efficacy and safety standards as an absolutely central issue in COVID-19 vaccine development are reassuring. By not telling which "unresolved issues" are meant in this paper, the reader might be misled by the author's out of context quotation.
Vanderlugt and Miller (2002)	"*These cytokines can induce autoantibody production through epitope spreading*"	The reference is focused on autoimmune and virus-induced immunity with no mention to post-vaccination autoimmunity and is thus irrelevant in the authors' assumptions context. «*Understanding the cellular and molecular basis of epitope spreading in various chronic immune-mediated human diseases [….] is crucial to understanding the pathogenesis of these diseases* » clearly does not refer to mRNA vaccines.
Simone et al. (2021)	"*COVID-19 vaccines cause myocarditis and pericarditis, with an increased risk in particular for men below the age of 50*"	No information about pericarditis in the provided reference which is therefore irrelevant to support the authors' claim. "*We evaluated acute myocarditis incidence and clinical outcomes among adults following mRNA vaccination in an integrated health care system in the US*."
Jain et al. (2021)	"*COVID-19 vaccines cause myocarditis and pericarditis, with an increased risk in particular for men below the age of 50*"	The study was not intended to identify and/or track pericarditis and was focused on the clinical and imaging characteristics of coronavirus disease 2019 vaccination–associated myocarditis. "*In this study, we aimed to characterize the clinical presentation, short-term prognosis, and myocardial tissue changes as noted on CMR or cardiac MRI in pediatric patients with coronavirus disease 2019 vaccination-associated myocarditis*.»
Choi et al. (2021), Verma et al. (2021)	"*Fatal cases of COVID-19 vaccination have been described*"	Two case reports of death occurring 5 days and 14 days after the first and the second dose of mRNA vaccine. Choi S. et al. conclude that "*The primary cause of death was determined to be myocarditis, causally-associated with the BNT162b2 vaccine*». Verma et al. mention that "*a direct causal relationship cannot be definitively established.*" Thus, no general conclusions can be drawn from these two cases. No published data support the hypothesis that SARS-CoV-2 vaccines could be a significant cause of fatal issues.
Wei et al. (2021)	"*Also, under conditions of overwhelming production of SARS-CoV-2 spike glycoprotein due to SARS-CoV-2 molecular vaccination, it would of course be expected that a significant proportion of over-abundant intracellular spike glycoproteins would also be exported via exosome cargoes*"	The paper mentions that "*exosomes bear specific repertoires of proteins and RNAs, indicating the existence of mechanisms that control the sorting of molecules into them*" which contradicts the author's claim.
No reference	"*Since these vaccines are specifically designed to induce high and ongoing production of SARS-CoV-2 spike glycoproteins, the implications are ominous*."	In a study on 13 healthy volunteers, S1 antigen was detected as early as day 1 postvaccination, and peak levels were detected on average 5 days after the first injection, with no S1 antigen detected at day 10 (Ogata et al., 2022). Spike protein was detectable in 3 of 13 participants an average of 15 days after the first injection. After the second vaccine dose, no S1 or spike antigen was detectable, and both antigens remained undetectable through day 56. Therefore, the assumption by Seneff et al. is wrong.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Jérôme Barrière*
Medical Oncology Department, Polyclinique Saint-Jean, Cagnes-sur-Mer, France

Fabrice Frank
Not Affiliated, Essaouira, Morocco

Lonni Besancon
Media and Information Technology, Linköping University, Norrköping, Sweden

Alexander Samuel
Not Affiliated, Grasse, France

Véronique Saada
Biopathology Department, Gustave Roussy Anticancer Canter, Villejuif, France

Eric Billy
Not Affiliated, Strasbourg, France

Abraham Al-Ahmad
Department of Pharmaceutical Sciences, Texas Tech University Health Sciences Center - Jerry H. Hodge School of Pharmacy, Amarillo, TX, United States

Nans Florens
Department of Nephrology, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Strasbourg, France

Barbara Seitz-Polski
Department of Immunology & UR2CA, Côte d'Azur University, CHU Nice, 151 Route Saint-Antoine de Ginestière, 06200, Nice, France

Jacques Robert
Université de Bordeaux, INSERM Unité 1312, 229 Cours de l'Argonne, 33076, Bordeaux, France

* Corresponding author.
E-mail address: docteurbarriere@outlook.fr (J. Barrière).

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